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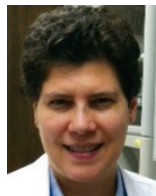
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Medication-Induced Hypokalemia

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INTRODUCTION

The cation potassium plays a critical role in many metabolic cell functions; 98% of potassium in the body is found in intracellular fluid compartments, leaving 2% in extracellular fluid spaces. This balance is regulated by the sodium-potassium adenosine triphosphatase (ATPase) pump, an active transport mechanism that moves ions across the cell membrane against a concentration gradient.^{1–5} An imbalance of potassium can have significant effects on nerve impulse transmission, skeletal and cardiac muscle contraction, and acid-base balances. Certain diseases, injuries, and specific medications have the potential to affect potassium homeostasis. As a result, small alterations in serum potassium levels can lead to detrimental effects within the body.

Normal serum potassium levels range from 3.5 to 5 mEq/L; however, certain hormones, illnesses, and dietary deficiencies can lead to imbalances, including acid-base disturbance, aldosterone, insulin, catecholamines, and tonicity of body fluids, as well as gastrointestinal (GI) and renal excretion. Daily intake of potassium is required because the body does not routinely conserve this electrolyte. The recommended daily requirement for adults is generally 40 mEq; how-

ever, most adults consume more than the recommended amount (ranging from 60 to 100 mEq per day). About 80% of consumed potassium is eliminated in the urine, 15% is excreted in the feces, and 5% is lost in sweat.^{3,4}

Hypokalemia is defined as a serum potassium concentration of less than 3.5 mEq/L. This is one of the most commonly encountered electrolyte abnormalities in clinical practice. Hypokalemia is further categorized as mild (serum potassium, greater than 3 to 3.5 mEq/L), moderate (serum potassium, 2.5 to 3 mEq/L), or severe (serum potassium, less than 2.5 mEq/L), as noted in Table 1.³ Hypokalemia results either when there is a total-body potassium deficit, or when serum potassium is shifted into the intracellular compartment.^{1–6} When hypokalemia is detected, a diagnostic workup that evaluates the patient's comorbid disease states and concomitant medications should be completed.

Table 1 reviews the signs and symptoms of hypokalemia. In mild cases of hypokalemia, patients are usually asymptomatic and are often diagnosed incidentally during routine blood testing. Moderate hypokalemia is often associated with cramping, weakness, malaise, and myalgias. In severe hypokalemia, electrocardiogram (ECG) changes often occur, including ST-segment depression or S-T-segment flattening, T-wave inversion, and/or U-wave elevation. These ECG changes can lead to various arrhythmias, including heart block, atrial flutter, paroxysmal atrial tachycardia, and ventricular fibrillation. Musculoskeletal cramping and impaired muscle contraction are other common manifestations of severe hypokalemia.^{1–4}

Hypomagnesemia, which is present in more than 50% of cases of clinically significant hypokalemia, contributes to the development of hypokalemia by reducing the intracellular potassium concentration and promoting renal potassium wasting.⁷ While the exact mechanism of the accelerated renal loss remains unclear, it is theorized that the intracellular potassium concentration may decrease because hypomagnesemia impairs the function of the sodium-potassium ATPase pump, thereby promoting potassium wasting. When concomitant hypokalemia and hypomagnesemia exist, the magnesium deficiency should be corrected first; otherwise, full repletion of the potassium deficit is difficult to achieve.

PATHOPHYSIOLOGY

Total-body potassium deficiencies are either secondary to inadequate intake or caused by excessive renal and GI fluid losses from diarrhea or vomiting. In cases of severe diarrhea and vomiting, metabolic alkalosis can occur and lead to an intracellular shifting of potassium, which further decreases the serum potassium concentration.⁴ Other potassium losses are seen in nephritis and renal tubular acidosis, Cushing's syndrome, and periods of high stress. Additional disorders that lead to potassium loss include hepatic disease, hyperaldosteronism, acute alcoholism, heart failure, Bartter's syndrome, and acute leukemias.^{1–8}

Medications cause hypokalemia through a variety of mechanisms, including intracellular potassium shifting, increased renal loss, and/or stool loss. Table 2 highlights selected medications associated with hypokalemia. Some published cases have reported an association

Table 1 Severity, Levels, and Symptoms of Hypokalemia^{1–4}

Severity	Level	Symptoms
Mild	> 3.0–3.5 mEq/L	Asymptomatic
Moderate	2.5–3.0 mEq/L	Cramping, malaise, myalgia, weakness
Severe	< 2.5 mEq/L	Electrocardiogram changes (including ST-segment depression, U-wave elevation, T-wave inversion), arrhythmias, paralysis

Disclosure: The authors report that they have no commercial or financial relationships in regard to this article.

Table 2 Selected Medications Associated With Hypokalemia^{1-5,13}

Medication Class	Examples of Common Drugs	Mechanism
Antimicrobials	<ul style="list-style-type: none"> • Nafcillin • Ampicillin • Penicillin • Aminoglycosides* • Amphotericin B* • Foscarnet* 	Renal potassium loss
Beta ₂ -receptor agonists	<ul style="list-style-type: none"> • Albuterol • Ephedrine • Epinephrine • Formoterol • Isoproterenol • Pseudoephedrine • Terbutaline • Salmeterol 	Shift of potassium from extracellular fluid to intracellular fluid compartment
Diuretics	<ul style="list-style-type: none"> • Acetazolamide • Bumetanide • Chlorthalidone • Ethacrynic acid • Furosemide • Indapamide • Metolazone • Thiazides • Torsemide 	Renal potassium loss
Insulin	High dose (overdose)	Shift of potassium from extracellular fluid to intracellular fluid compartment
Mineralocorticoids and glucocorticoids	<ul style="list-style-type: none"> • Hydrocortisone[†] • Fludrocortisone • Prednisone[†] 	Renal potassium loss
Laxatives	<ul style="list-style-type: none"> • Sodium polystyrene sulfonate • Phenolphthalein • Sorbitol 	Stool (gastrointestinal) potassium loss
Xanthines	<ul style="list-style-type: none"> • Theophylline • Caffeine 	Shift of potassium from extracellular fluid to intracellular fluid compartment
Other	Verapamil (in overdose)	Shift of potassium from extracellular fluid to intracellular fluid compartment

* Also associated with magnesium depletion

[†] Increases potassium excretion nonspecifically through effect on filtration rate and distal sodium delivery

between antidepressant use and the risk for hypokalemia. This adverse effect may put psychiatric patients at risk.^{4,9,10} Further studies are required to elucidate a possible association between selective serotonin reuptake inhibitors and hypokalemia. Additionally, a few case reports have noted a risk for hypokalemia with the use of iodinated contrast.¹¹ In these cases, iodinated contrast-induced hyperthyroidism leads to thyrotoxic periodic

paralysis. Up to 32% of acute hypokalemia paralysis is thyrotoxic in nature. The overstimulation of the sodium-potassium ATPase pump by thyroid hormones during thyrotoxic paralysis leads to an acute intracellular shift of potassium into the cells, causing a hypokalemic medical emergency.

In the geriatric population, medication-induced hypokalemia is very common.¹² Diuretics are a particularly troublesome

source of medication-induced effects in the elderly. Decreased dietary potassium intake, diminished renal reserve, altered pharmacokinetics/pharmacodynamics due to concurrent disease (e.g., congestive heart failure, renal failure), concomitant therapies (e.g., glucocorticoids), and use of high-dose, long-acting thiazide diuretics are among the factors that contribute to diuretic-induced hypokalemia in the elderly.

PRINCIPLES OF TREATMENT AND REPLACEMENT

Treatment for hypokalemia focuses on restoring a normal potassium balance, preventing serious complications, and removing or treating the underlying cause(s).³ Management strategies vary depending on the severity of the imbalance (see Table 3). Serum potassium concentrations between 3.5 and 4 mEq/L are a sign of early potassium depletion. No pharmacological therapy is recommended at this point, but the patient's diet should be assessed. Most cases of mild-to-moderate hypokalemia may be corrected with oral potassium supplements. Potassium chloride (KCl) is the most common salt used for repletion. Potassium acetate is a preferred agent in patients with hypokalemia and metabolic acidosis. Administration of potassium phosphate should be considered in patients with hypokalemia and hypophosphatemia.¹⁻³

Patients who have severe hypokalemia or who cannot take oral supplements require intravenous (IV) potassium replacement therapy. IV potassium must be administered with caution to prevent serious complications, including potentially fatal cardiac arrhythmias. All infusions should be diluted and mixed thoroughly in adequate amounts of fluid; use premixed potassium solutions when possible. To prevent or reduce toxic effects, IV infusion concentrations should not exceed 40 mEq/L and should be infused at a rate of 10 mEq per hour or less. Cardiac monitoring is essential with potassium administration at a rate of 20 mEq per hour or higher. Frequent serum potassium assessment is vital during potassium administration and should be performed every one to three hours.^{1,3,4,8} A general rule for replacement in patients with normal renal function is 10 mEq KCl administration, which will raise the

Table 3 Hypokalemia Treatment³

Severity	Treatment	Types
Mild, moderate, and asymptomatic hypokalemia	<ul style="list-style-type: none"> Supplement with oral therapy; if patient is not tolerating oral medications, IV therapy would be indicated as an alternative. After using immediate-release preparations, check potassium levels in at least 60 minutes. After using a sustained-release product, check potassium levels in at least 3 hours. 	<ul style="list-style-type: none"> Potassium chloride: Klor-Con extended-release tablets, immediate-release packets, Upsher-Smith; K-tab extended release tablets, AbbVie; Phos-NaK powder concentrate, Cypress Pharma Potassium phosphate:* Neutra-Phos packets, Janssen; K-Phos Neutral tablets, Beach Pharma Potassium bicarbonate:† Effer-K tablet, Nomax; K-Bicarb capsule, Bio-Tech
Severe and symptomatic hypokalemia	<ul style="list-style-type: none"> IV supplementation is recommended: 10–20 mEq per hour diluted in 100 mL NS. 10 mEq may be given peripherally. If > 10 mEq/hour, give centrally and monitor electrocardiogram. Re-evaluate serum potassium level after 30–40 mEq is infused. Serum potassium levels should be obtained 30 minutes after the end of the infusion. Avoid sampling from the line where the potassium is infusing. Patients needing potassium of 300–400 mEq/day can receive 40–60 mEq in 1 L 0.45% NS not faster than 40 mEq/hour in an ICU setting through a central IV line into a large vein to prevent burning pain and peripheral venous sclerosis. IV doses should be prepared following USP 797 standards, or use commercially available IV piggyback or large-volume parenteral bags. Alternatively, if larger doses are needed, oral therapy can be used adjunctively with IV therapy to split the total dose. Do not use sustained-release preparations when an immediate result is needed. 	<ul style="list-style-type: none"> Potassium chloride: various concentrations Potassium phosphate: 15 mmol in 100 mL D5W (15 mmol potassium provides approximately 22 mEq of potassium) over 2 hours in an ICU and over 4–6 hours outside the ICU setting; 3 mmol potassium phosphate can also be administered in 100 mL D5W over 1 hour and repeated if needed Potassium acetate: IV formulation of potassium bicarbonate

* Preferred in patients with hypokalemia and hypophosphatemia
† Preferred in patients with hypokalemia and metabolic acidosis
ICU = intensive care unit; IV = intravenous; NS = normal saline

serum potassium level by 0.1 mmol/dL.³

A patient taking a thiazide or loop diuretic may be switched to a potassium-sparing agent like spironolactone (Aldactone, Pfizer), eplerenone (Inspra, Pfizer), triamterene (Dyrenium, WellSpring Pharmaceuticals), or amiloride (Midamor, Merck) to prevent excessive urinary potassium loss. Spironolactone and eplerenone are effective as potassium-sparing agents in patients with primary or secondary hyperaldosteronism. Eplerenone has been associated with fewer side effects because of its lower affinity for sex-hormone receptors, which leads to a reduced incidence of gynecomastia compared with spironolactone therapy. Amiloride by an aldosterone-independent mechanism.^{1,3,4,8}

After the serum potassium level returns to normal, a sustained-release oral potassium supplement may be required with daily dosages ranging from 20 mEq to 80 mEq. Patients may

also need to increase their dietary intake of potassium-rich foods, such as dried fruits (e.g., dates, prunes, figs), nuts, avocados, bran cereals, spinach, potatoes, kiwi, and bananas. Daily supplementation with potassium is required for patients who continue to take medications that can lead to hypokalemia; such supplementation should be stopped when these medications are discontinued. Additionally, if a patient's medical condition leads to acute hypokalemia, short-term repletion is necessary. However, continuation of potassium supplementation is not generally required after the illness has been treated. Many patients are concomitantly prescribed medications that both increase and decrease potassium levels. Often the overall effect on the potassium level is null and supplementation is not necessary. For example, patients with cardiac dysfunction will require a loop diuretic and an angiotensin-converting enzyme inhibitor for maintenance therapy. Since

these medications, given together, have opposing effects on potassium levels, supplementation may not be required to maintain optimal levels.

A case of medication-induced hypokalemia recently seen at our hospital is described below.

Case Report

A 58-year-old female presented to the emergency department with a chief complaint of ongoing fatigue and weakness. She had noticed a gradual increase in symptoms over the past two weeks. She had required more frequent rest breaks during that time than she had in the past, with intermittent episodes of dyspnea. Upon further questioning, she complained of intermittent nausea leading to decreased appetite. She had been hospitalized three months earlier for newly diagnosed acute adrenal insufficiency, which was treated with IV hydrocortisone and fluid replacement. The IV hydrocortisone dose had been tapered to

an oral maintenance dose. Fludrocortisone (Florinef, Pfizer) 0.1 mg orally (PO) daily was added because she remained hyperkalemic despite hydrocortisone maintenance therapy. Her home medications included hydrocortisone 20 mg (Cortef, Pfizer) orally every morning and 10 mg orally every evening, and fludrocortisone 0.1 mg orally every morning, along with an oral multivitamin.

During the admission to our hospital, her blood pressure was 110/76 mm Hg, her pulse was 82 beats per minute, and her respiratory rate was 20 breaths per minute. Her potassium level was measured at 2.9 mEq/L (normal, 3.5–5 mEq/L) and her white blood cell count was elevated to 14.9 x 1,000 cells/mm³ (normal, 5–10 x 1,000 cells/mm³). All other laboratory values were within normal ranges. Her lungs had decreased breath sounds on the left side, compared to the right side with rales. Her oxygen saturation was 92% on room air. Her laboratory tests, signs, and symptoms were consistent with community-acquired pneumonia, including a fever of 99.3° F, shortness of breath, and a chest x-ray that was positive for left lower lobe infiltrates. Her CURB-65 score was 1, but her recent comorbidity warranted her hospital admission.¹⁴ The CURB-65 score is a validated tool used in predicting mortality in patients with community-acquired pneumonia (see Table 4).¹⁴ One point is given for each of the following features: confusion (mental test score of 8 or less, new disorientation in person, place, or time); blood urea nitrogen greater than 20 mg/dL; a respiratory rate of 30 breaths per minute or more; systolic blood pressure (BP) of less than 90 mm Hg or diastolic BP of 60 mm Hg or less; and age 65 years or more.

With a presumed diagnosis of commu-

Table 4 CURB-65 Score Assessment ¹⁴		
Score	Risk Assessment	Treatment
0–1	Low risk	Outpatient (risk of death < 3%)
2	Moderate risk	Inpatient hospitalization (risk of death ~9%)
3–5	Severe risk	Intensive care unit inpatient hospitalization required (risk of death 15–40%)

nity-acquired pneumonia, empiric antibiotics consisting of ceftriaxone (Rocephin, Roche) 1 g IV daily for seven days and azithromycin (Zithromax, Pfizer) 500 mg PO daily for three days were initiated and potassium replacement was added to correct the hypokalemia. It was presumed that the hypokalemia was secondary to infection and dehydration. After three days of potassium chloride 10 mEq IV three times a day, the clinical pharmacist was consulted for evaluation of persistent hypokalemia. The potassium levels are noted in Table 5. Upon medication review, the clinical pharmacist recommended holding the fludrocortisone. Twice-daily glucocorticoids were used to mimic physiological patterns. After three days without fludrocortisone, therapeutic potassium levels were achieved and additional potassium supplementation was not required. She was counseled not to resume fludrocortisone, and, since she was no longer hypokalemic, chronic potassium supplementation was not needed.

DISCUSSION

Addison’s disease occurs when the adrenal glands produce insufficient levels of hormones, particularly mineralocorticoid and glucocorticoid steroids. Patients with this endocrinological disorder generally present with fatigue, weight loss, orthostatic hypotension, hyperpigmen-

tation of the skin, hyperkalemia, and hyponatremia. Treatment of Addison’s disease focuses on replacement of cortisol and aldosterone.¹⁵ Although hydrocortisone can function as a replacement for both of these hormones, the addition of fludrocortisone is often necessary to help ensure electrolyte balance. However, close monitoring of electrolyte levels is warranted, especially for potassium, since combination therapy may result in hypokalemia, as occurred in our patient.¹⁵ In this case, the medical team appeared to have missed the etiology of the hypokalemia because medication-induced hypokalemia was not on their differential list. Her hypokalemia was thought to be related to dehydration; however, after continuous potassium repletion and rehydration, her potassium levels remained low, and additional etiologies were discussed.

Determining the etiology of the hypokalemia is essential in order to appropriately manage patients. As previously noted, hypokalemia can be caused by medical conditions, acute illnesses, or medications. It is important to explore each potential cause for every patient who presents with hypokalemia. In this case, due to the mineralocorticoid properties of fludrocortisone, persistent potassium loss occurred despite continued potassium repletion. It was not until fludrocortisone

Table 5 Progression of Abnormal Laboratory Values and Potassium Therapy Management							
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
K+ (mEq/L) Normal range: 3.5–5 mEq/L	2.9, L	3.1, L	3.0, L	3.0, L	3.2, L	3.4, L	3.8
White blood cells (1,000 cells/mm ³) Normal range: 5–10 x 1,000 cells/mm ³	14.2, H	13.8, H	12.4, H	11.9, H	9.6	9.2	8.5
Intervention	IV KCl 10 mEq, 3 doses	IV KCl 10 mEq, 3 doses	IV KCl 10 mEq, 3 doses	Held fludro- cortisone, IV KCl stopped	Held fludro- cortisone	Held fludro- cortisone	Discontinued fludrocortisone; patient discharged

L = low potassium; H = high white blood cells; IV = intravenous; KCl = potassium chloride

was discontinued that the potassium level increased and returned to the normal range.

CONCLUSION

In the absence of early detection and treatment, hypokalemia can cause serious complications that could be life-threatening. The vast majority of hypokalemia cases are drug-induced, as was finally evident in this case. Our patient exhibited profound hypokalemia with significant symptoms. Fortunately, the etiology was identified relatively early in her hospitalization. As clinical pharmacists monitoring patient therapy, we must be vigilant in identifying potentially drug-induced disease as early as possible. In doing so, we can assist in early treatment interventions to improve patient outcomes and decrease lengths of stay while preventing untoward reactions and associated medical complications. After discontinuation of the fludrocortisone, potassium levels remained at therapeutic levels and the patient remained asymptomatic. No further potassium treatment was needed.

REPORTING ADVERSE DRUG REACTIONS

All adverse drug reactions (ADRs) should be reported to MedWatch at 1-888-INFO-FDA, 1-888-463-6332, or online. The FDA 3500 Voluntary Adverse Event Report Form can easily be accessed online for reporting ADRs at www.fda.gov/Safety/Medwatch/HowToReport/ucm085568.htm.

The FDA is interested in serious reports that include any of the following patient outcomes: death; life-threatening condition; initial hospitalization; prolonged hospitalization; disability or permanent damage; congenital anomalies or birth defects; and other serious conditions for which medical or surgical intervention is needed to prevent one of the aforementioned outcomes. In addition, the FDA is interested in any unlabeled ADRs for new drugs (e.g., usually those approved within the previous two years).

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